

<b>DECLARATION OF YASUMICHI HITOSHI UNDER 37 C.F.R. §1.131</b>	Application Number	09/843,159
	Confirmation Number	8575
	Filing Date	April 25, 2001
	First Named Inventor	Ying Luo
	Examiner	Manjunath Rao
	Group Art	1652
	Attorney Docket No.	RIGL-010CIP2

This Declaration with the attached Exhibits are being submitted in conjunction with the Applicants' Response to the Office Action dated May 26, 2004.

I, Yasumich Hitoshi, M.D. Ph.D., do hereby declare as follows.

1. I am currently a program director at Rigel Pharmaceuticals, Inc. (hereinafter "Rigel"), and the work described in the above-referenced patent application was performed with my knowledge.
2. I understand that the claimed subject matter of the above-referenced patent application relates to assays for identifying agents that modulate the poly(A) ribose polymerase activity of Tankyrase H.
3. I have been asked to provide factual evidence relating to the activities of Rigel and Rigel's patent counsel with respect to the claimed subject matter, prior to October 25, 1999 (the filing date of the above-referenced patent application).

4. I have reviewed the Exhibits attached hereto and they all relate to the activities of Rigel or Rigel's patent counsel with respect the claimed subject matter, prior to October 25, 1999.
5. Prior to June 11, 1999, the inventors of the above-referenced patent application identified the sequence of the ADP-ribose polymerase domain of Tankyrase H and identified that Tankyrase H had poly(A) ribose polymerase activity. Evidence for this is provided in Exhibit A. All redacted dates are prior to June 11, 1999.
6. Further, between June 11, 1999, and July 21 1999, the inventors worked towards identifying the full length sequence of Tankyrase H for use in the above-referenced screening assays. Evidence for this is provided in Exhibits B and C. The dates have not been redacted in these exhibits.
7. Finally, between July 20, 1999 and October 25, 1999, the above-referenced patent application was drafted at the law firm of Flehr, Hobach, Test, Albritton and Herbert (hereinafter "Flehr"), the law firm contracted to draft the above-referenced patent application. Evidence for this is provided in Exhibits D – H. The dates have not been redacted in these exhibits.
8. Exhibit A consists of a print-out of Tankyrase H amino acid and nucleic acid sequences. On pages, 2, 6 and 7 of this Exhibit, Tankyrase H is identified as having a poly(A) ribose polymerase domain. The date of the print-out was prior to June 11, 1999.
9. Exhibit B consists of a presentation that was made by Xiang Xu, an inventor, that identifies Tankyrase H as having poly(A) ribose polymerase activity on page 3. The date of this presentation was June 15, 1999.
10. Exhibit C consists of signed laboratory notebook pages from Simon Yu, a colleague at Rigel Pharmaceuticals, Inc. These notebook pages show results of experiments directed towards identifying the full length sequence of Tankyrase H for use in the above-


referenced screening assays. The notebook pages are dated July 9, July 13, July 15, July 16 and July 21, 1999, respectively.

11. Exhibit D consists of a letter from Nicole Verona of Rigel to Ms. Robin Silva of Flehr), the law firm contracted to draft the above-referenced patent application. The letter references an invention disclosure (i.e., eight packages of information) for use in preparation of the above-referenced patent application. The date of the letter is July 20, 1999.
12. Exhibit E consists of a letter from Nicole Verona of Rigel to Ms. Robin Silva of Flehr. The letter references diskettes for use in preparation of the above-referenced patent application. The date of the letter is July 22, 1999.
13. Exhibit F consists of a file information page from Flehr, indicating that the file for the above-referenced patent application was opened on July 26, 2003.
14. Exhibit G consists of an e-mail dated August 30, 1999, from Nicole Verona of Rigel to Ms. Dolly Vance of Flehr regarding questions about the above referenced invention disclosure. The body of this e-mail contains text of previous e-mails dated August 20, 1999 and August 26, 1999, also relating to the above referenced invention disclosure.
15. Exhibit H consists of a letter from Nicole Verona of Rigel to Ms. Dolly Vance regarding further documents for use in drafting the above-referenced patent application. The date of the letter is September 30, 1999.
16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

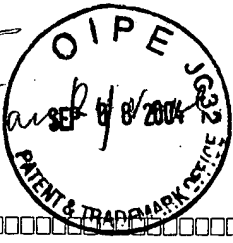
of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: 9/3/04

  
Yasumichi Hitoshi, M.D. Ph.D.,

Attachments: Exhibits A - G



final

Exhibit A 09/843,159

in xxu common

Seqn fold from 1/19

Longest ORF frame 1 of 1060 amino acids  
From amino acid position 84 to 1143

1 MVQTPMLEIIGIILLSMKLQKLERLMFALCCYFAVLLQHGAEPTILNTDGRTALDLADPS  
61 AKAVLTGEYKKDELLESARSGNEEKMMALLTPLNVNCHASDGRKSTPLHLAAGYNRVKIV  
121 QLLLQHGADVHAKDKGDLVPLHNACSYGHYEVTPELLVKHGACVNAMDLWQFTPLHEAASK  
181 NRVEVCSLLLSYGADPTLLNCHNKSADLAPTQPKERLAYEFKGHSLQAAREADVTRI  
241 KKHLSLEMVNFKHPQTHETALHCAAASPYPKRKQICELLRLKGANINEKTKEFLTPLHVA  
301 SEKAHNDVVEVVVKHEAKVNALDNLGQTSLHRAAYCGHLQTCRLLLSYGCDPNIIISLQGF  
361 TALQMGNNENVQQLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQS  
421 TPLHFAAGYNRVSVVEYLLQHGADVHAKDKGLVPLHNACSYGHYEVAELLVKHGAVVNV  
481 ADLWKFTPLHEAAAKGKYEICLLLLQHGADPTKKNRDGNTPLDLVKDGDTDIHYLLRGDA  
541 ALLDAAKKGCLARVKKLSSPDNVNCRDTQGRHSTPLHLAAGYNNLEVAEYLLQHGADVNA  
601 QDKGGLIPLHNAASYGHVDVAALLIKYNACVNATDKWAFTPLHEAAQKGRQTQLCALLLAH  
661 GADPTLKNQEGQTPLDLVSADDVSALLTAAMPSPALPSCYKPQVLNGVRSFGATADALSS  
721 GPSSPSSLSAASSLDNLSGSFSELSSLVSSSGTEGASSLEKKEVPGVDFSITQFVRNLGL  
781 EHLMDIFEREQITLDVLVEMGHKELKEIGINAYGHRHKLKIGVERLISGQQGLNPYLTLN  
841 TSGSGTILIDLSPDDKEFQSVVEEMQSTVREHRDGGHAGGIFNRYNLIKIQKVCNKKLWE  
901 RYTHRRKEVSEENHNHANERMLFHGSPFVNAIHKGFDERHAYIGMFGAGIYFAENSSK  
961 SNQYVYGIGGGTGC PVHKDRSCYICHRQLLFCRVTLGKSFLQFSAMKMAHSPPGHHSVTG  
1021 RPSVNLALAEYVIYRGEQAYPEYLITYQIMRPEGMVDGZ

1 GAAGTGCAGCGGGGTGGATTTCTCTGGAATTGCCTTAGTAGTAGTACCACCCAAGGCACTG  
61 CTTAGGTACCCTGCTGCTTAGTGAGAGTCCCTCTGGCTTTATCATTAAAGGTTTGGGC  
121 GGAAAGACGTAGTTGAATATTTGCTTCAGAATGGTGCAAATGTCCAAGCACGTGATGATG  
181 GGGGCCCTTATTCCTCTTCATAATGCATGCTCTTTTGGTCATGCTGAAGTAGTCAATCTCC  
241 TTTTGGCAGATGGTGAGAGCCCAATGCTCGAGATAATTGGAATTATACTCCTCTCCATG  
301 AAGCTGCAATTAAAGGAAAGATTGATGTTTGCATTGTGTGCTATTTTGCAGTGTGTTA  
361 CAGCATGGAGCTGAGCCAACCATCTAAATACAGATGGAAGGACAGCATTTGGATTTAGCA  
421 GATCCATCTGCCAAAGCAGTGTCTACTGGTGAATATAAGAAAGATGAACCTTTAGAAAGT  
481 GCCAGGAGTGGCAATGAAGAAAAAATGATGGCTCTACTCACACCATTAAATGTCAACTGC  
541 CACGCAAGTGATGGCAGAAAGTCAACTCCATTACATTTGGCAGCAGGATATAACAGAGTA  
601 AAGATTGTACAGCTGTTACTGCAACATGGAGCTGATGTCCATGCTAAAGATAAAGGTGAT  
661 CTGGTACCATTACACAATGCCCTGTTCTTATGGTCAATTATGAAGTAACTGAACTTTGGTC  
721 AAGCATGGTGCTGTGTAATGCAATGGACTTGTGGCAATTCACCTCTTTCATGAGGCA  
781 GCTTCTAAGAACAGGGTTGAAGTATGTTCTCTTCTCTTAAGTTATGGTGCAGACCCAACA  
841 CTGCTCAATTGTCAATAAAAGTGCTATAGACTTGGCTCCACACCACAGTTAAAGAA  
901 AGATTAGCATATGAATTTAAAGGCCACTCGTTGCTGCAAGCTGCACGAGAAGCTGATGTT  
961 ACTCGAATCAAAAAACATCTCTCTGGAATGGTGAATTTCAAGCATCCTCAACACAT  
1021 GAAACAGCATTCATTGTGCTGCTGCATCTCCATATCCCAAAGAAAGCAAATATGTGAA  
1081 CTGTTGCTAAGAAAAGGAGCAAAACATCAATGAAAAGACTAAAGAATTCTTGACTCCTCTG  
1141 CACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACATGAAGCA  
1201 AAGGTTAATGCTCTGGATAATCTTGGTCAAGCTTCTCTACACAGAGCTGCATATTGTGGT  
1261 CATCTACAAACCTGCCGCTACTCCTGAGCTATGGGTGTGATCCTAACATTATATCCCTT  
1321 CAGGGCTTTACTGCTTTACAGATGGGAAATGAAAATGTACAGCAACTCCTCCAAGAGGGT  
1381 ATCTCATTAGGTAATTCAGAGGCAGACAGACAATTGCTGGAAGCTGCAAAGGCTGGAGAT  
1441 GTCGAAACTGTAAAAAACTGTGTACTGTTCAAGTGTCAACTGCAGAGACATTGAAGGG  
1501 CGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTGGAATAT  
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1681 GTTAATGTAGCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAAGGAAAA  
1741 TATGAAATTTGCAAACTTCTGCTCCAGCATGGTGCAGACCCCTACCAAAAAAACAGGGAT  
1801 GGAAATACTCCTTTGGATCTTGTAAAGATGGAGATACAGATATTCATTATCTGCTTAGG  
1861 GGAGATGCAGCTTTGCTAGATGCTGCCAAGAAGGGTTGTTTAGCCAGAGTGAAGAAGTTG  
1921 TCTTCTCTGATAATGTAAATTGCCGCGATACCCAAGGCAGACATTCAACACCTTTACAT

1981 TTAGCAGCTGGTTATAATAATTTAGAAAGTTGCAGAGTATTTGTTACAACACGGAGCTGAT  
 2041 GTGAATGCCCAAGACAAAGGAGGACTTATTCCTTTACATAATGCAGCATCTTACGGGCAT  
 2101 GTAGATGTAGCAGCTCTACTAATAAAGTATAATGCATGTGTCAATGCCACGGACAAATGG  
 2161 GCTTTTCACACCTTTTGACGAAGCAGCCAAAAGGGACGAACACAGCTTTGTGCTTTGTTG  
 2221 CTAGCCCATGGAGCTGACCCGACTCTTAAAAATCAGGAAGGACAAACACCTTTAGATTTA  
 2281 GTTTCAGCGGATGATGTCAGCGCTCTTCTGACAGCAGCCATGCCCCATCTGCTCTGCCC  
 2341 TCTTGTTACAAGCCTCAAGTGCTCAATGGTGTGAGAAGCCCAGGAGCCACTGCAGATGCT  
 2401 CTCTCTTCAGGTCCATCTAGCCCATCAAGCCTTTCTGCAGCCAGCAGTCTTGACAACTTA  
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 2581 CTTGGACTTGAGCACCTAATGGATATATTTGAGAGAGAACAGATCACTTTGGATGTATTA  
 2641 GTTGAGATGGGGCACAAGGAGCTGAAGGAGATTGGAATCAATGCTTATGGACATAGGCAC  
 2701 AAACATAATTAAAGGAGTCGAGAGACTTATCTCCGGACAACAAGGCTTAACCCATATTTA  
 2761 ACTTTGAACACCTCTGGTAGTGGAACAATTCTTATAGATCTGTCTCCTGATGATAAAGAG  
 2821 TTTCAGTCTGTGGAGGAAGAGATGCAAAGTACAGTTTCGAGAGCACAGAGATGGAGGTCAT  
 2881 GCAGGTGGAATCTTCAACAGATACAAATATTTCTCAAGATTTCAGAAGGTTTGTAAACAAGAA  
 2941 CTATGGGAAAGATACTCACCAGGAGAAAAAGGTTTCTGAAGAAAACCACAACCATGCC  
 3001 AATGAACGAATGCTATTTTCATGGGTCTCCTTTTGTGAATGCAATTATCCACAAAGGCTTT  
 3061 GATGAAAGGCATGCCGTACATAGGTGGTATGTTTGGAGCTGGCATTATTTTGTGTAAGAAC  
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 3181 AAAGACAGATCTTGTACATTTGCCACAGGCAGCTGCTCTTTTGGCCGGGTAACCTTGGA  
 3241 AAGTCTTTCTCGAGTTTCAAGTGCAATGAAAATGGCACATTCTCTCCAGGTCATCACTCA  
 3301 GTCAGTGGTAGGCCAGTGTAAATGGCTTAGCATTAGCTGAATATGTTATTTACAGAGGA  
 3361 GAACAGGCTTATCTGAGTATTTAATTACTTACCAGATTATGAGGCCTGAAGGTATGGTC  
 3421 GATGGATAAATAGTTATTTTAAAGAACTAATTCACCTGAACCTAAAATCATCAAAGCAGC  
 3481 AGTGGCCTCTACGTTTTTACTCCTTTTGCTGAAAAA

ref|NP\_003738.1|PTNKS| TANKYRASE >gi|3929219 (AF082556) TRF1-interacting  
 ankyrin-related

ADP-ribose polymerase [Homo sapiens] Length = 1327  
 Score = 1640 bits (4199), Expect = 0.0  
 Identities = 790/1023 (77%), Positives = 871/1023 (84%), Gaps = 11/1023 (1%)  
 Query: 35 VLLQHGAEPITLNTDGRALDLADPSAKAVLTGEYKKDELLESARSGNEEKMMALLTPLN 94  
 VLLQHGA+P I NTDG++ALDLADPSAKAVLTGEYKKDELLE+ARSGNEEK+MALLTPLN  
 Sbjct: 300 VLLQHGAADPNIRNTDGRKSLDLADPSAKAVLTGEYKKDELLEAARSNGNEEKLMMALLTPLN 359  
 Query: 95 VNCHASDGRKSTPLHLAAGYNRVKIVQLLLQHGAADVHAKDKGDLVPLHNACSYGHYEVE 154  
 VNCHASDGRKSTPLHLAAGYNRV+IVQLLLQHGAADVHAKDKG LVPLHNACSYGHYEVE  
 Sbjct: 360 VNCHASDGRKSTPLHLAAGYNRVRIQLLLQHGAADVHAKDKGGLVPLHNACSYGHYEVE 419  
 Query: 155 LLVKHGACVNAMDLWQFTPLHEAASKNRVEVCSLLLSYGADPTLLNCHNKSALDLAPTQ 214  
 LL+KHGACVNAMDLWQFTPLHEAASKNRVEVCSLLLS+GADPTL+NCH KSA+D+APTQ+  
 Sbjct: 420 LLLKHGACVNAMDLWQFTPLHEAASKNRVEVCSLLLSHGADPTLVNCHGKSAVDMAPTPE 479  
 Query: 215 LKERLAYEYFKGHSLLQAAREADVTRIKKHLSEMVNFKHPQTHETALHCAAASPYPKRKQ 274  
 L+ERL YEFKGHSLLQAAREAD+ ++KK L+LE++NFK PQ+HETALHCA AS +PKRKQ  
 Sbjct: 480 LRERLTYEFKGHSLLQAAREADLAKVKKTLALEIINFKQPQSHETALHCAVASLHPKRKQ 539  
 Query: 275 ICELLLRKGANINEKTKFLTPLHVASXXXXXXXXXXXXXXXXXXXXXLDNLGQTSLHRAA 334  
 + ELLLRKGAN+NEK K+F+TPLHVA+ LD LGQT+LHRAA  
 Sbjct: 540 VTELLLRKGANVNEKNKDFMTPLHVAAERAHNDVMEVLHKHGAKMNALDTLGQTLHRAA 599  
 Query: 335 YCGHLQTCRLLLSYGCDPNIISLQGFTALQMGNEENVQQLLQEGISLGNSEADRQLLEAAK 394  
 GHLQTCRLLLSYG DP+IISLQGFTA QMGNE VQQ+L E + S+ D +LLEA+K  
 Sbjct: 600 LAGHLQTCRLLLSYGSDPSIISLQGFTAAQMGNEAVQQILSESTPIRTSDVDYRLLLEASK 659



121 GCCAAAGCAGTGCCTTACTGGTGAATATAAGAAAGATGAACCTTTAGAAAGTGCCAGGAGT  
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1 GGCACGAGCTGCAACGAAATGGAAAGATTGATGTTTTGCATTGTGTTTACAGCATGGA  
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 2521 GTGGAGGAAGAGATGCAAAGTACAGTTCGAGAGCACAGAGAF7TGGAGGTCATGCAGGTGGA  
 2581 ATCTTCAACAGATACAATATTCTCAAGATTGAGAAGGTTTGTAACA  
 Plus  
 3'end

GTCTCCTGATGATAAAGAGTTTTCAGTCTGTGGAGGAAGAGATGCAAAGT  
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 ATGGATAAATAGTTATTTTAAAGAACTAATTCCTGAACCTAAAATCATCAAAGCAGC  
 AGTGGCCTCTACGTTTTACTCCTTTGCTGAAAAA

gi|3929219 (AF082556) TRF1-interacting ankyrin-related ADP-ribose polymerase  
[Homo sapiens] Length = 1327

Score = 464 bits (1181), Expect = e-130

Identities = 223/309 (72%), Positives = 249/309 (80%) Frame = +2

Query: 2 LEMVNFKHPQTHETALHCAAASPYPKRKQICELLRLKGANINEKTKEFLTPLHVASXXXX 181  
LE++NFK PQ+HETALHCA AS +PKRKQ+ ELLRLKGAN+NEK K+F+TPLHVA+  
Sbjct: 511 LEIINFKQPQSHETALHCAVASLHPK RKQVTELLRLKGANVNEKNKDFMTPLHVAAERAH 570

Query: 182 XXXXXXXXXXXXXXXXLDNLGQTS LHRAAYCGHLQTCRLLLSYGCDPNIIISLQGFTALQM 361  
LD LGQT+LHRAA GHLQTCRLLLSYG DP+IISLQGFTA QM  
Sbjct: 571 NDVMEVLHKHGAKMNALDTLGQTALHRAALAGHLQTCRLLLSYGSDPSIIISLQGFTAAQM 630

Query: 362 GNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQSTPLHF 541  
GNE VQQ+L E + S+ D +LLEA+KAGD+ETVK+LC+ Q+VNCRD+EGR STPLHF  
Sbjct: 631 GNEAVQQLLSESTPIRTSDVDYRLLEASKAGDLETVKQLCSSQNVNCRDLEGRHSTPLHF 690

Query: 542 AAGYNRVSVVEYLLQH GADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAVNVNADLWK 721  
AAGYNRVSVVEYLL HGADVHAKDKGGLVPLHNACSYGHYEVAELLV+HGA VNVADLWK  
Sbjct: 691 AAGYNRVSVVEYLLHHGADVHAKDKGGLVPLHNACSYGHYEVAELLVRHGASVNVNADLWK 750

Query: 722 FTPLHEAAAKGKYEICKLLLQH GADPTKKNRDGNTPDLVKDGD TXIQXXXXXXXXXXXXX 901  
FTPLHEAAAKGKYEICKLLL+HGADPTKKNRDGNTPDLVK+GDT IQ  
Sbjct: 751 FTPLHEAAAKGKYEICKLLLKHGADPTKKNRDGNTPDLVKEGD TDIQDLLKGDAALLDA 810

Query: 902 XXKGCFXQI 928  
KGC ++

Sbjct: 811 AKKGCLARV 819

Longest ORF frame 2 of 310 amino acids

From amino acid position 1 to 311

1 LEMVNFKHPQTHETALHCAAASPYPKRKQICELLRLKGANINEKTKEFLTPLHVASEKAH  
61 NDVVEVVVKHEAKVNALDNLGQTS LHRAAYCGHLQTCRLLLSYGCDPNIIISLQGFTALQM  
121 GNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQSTPLHF  
181 AAGYNRVSVVEYLLQH GADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAVNVNADLWK  
241 FTPLHEAAAKGKYEICKLLLQH GADPTKKNRDGNTPDLVKDGD TXIQDLLRGDAXXLLDA  
301 AXKGCFXQIX

1 GCTGGAAATGGTGAATTTCAAGCATCCTCAAAR7CACATGAAACAGCATTGCATTGTGCTGC  
61 TGCATCTCCATATCCCAAAAGAAAGCAAAR6TATGTGAAC TGTGCTAAGAAAAGGAGCAAA  
121 R5CATCAATGAAAAGACTAAAGAAATTC TTGACTCCTCTGCACGTGGCATCTGAGAAAGCTCA  
181 TAATGATGTTGTTGAAGTAGTGGTGAACATGAAGCAAAGGTTAATGCTCTGGATAATCT  
241 TGGTCAGACTTCTCTACACAGAGCTGCATATTGTGGTCATCTACAAACCTGCCGCC TACT  
301 CCTGAGCTATGGGTGTGATCCTAACATTATATCCCTTCAGGGCTTTACTGCTTTACAGAT  
361 GGGAAATGAAAATGTACAGCAACTCCTCCAAGAGGGTATCTCAT TAGGTAATTCAGAGGC  
421 AGACAGACAATTGCTGGAAAGCTGCAAAGGCTGGAGATGTCGAAACTGTAAAAAACTGTG  
481 TACTGTTTACAGAGTGTCAACTGCAGAGACATTGAAGGGCGTCAGTCTACACCACTTCATTT  
541 TGCAGCTGGGTATAACAGAGTGTCCGTGGTGAATATCTGCTACAGCATGGAGCTGATGT  
601 GCATGCTAAAGATAAAGGAGGCC TTTGTACCTTTGCACAATGCATGTTCTTATGGACATTA  
661 TGAAGTTGCAGAACTTCTTGTAAACATGGAGCAGTAGTTAATGTAGCTGATTTATGGAA  
721 ATTTACACCTTTTACATGAAGCAGCAGCAAAAGGAAAATATGAAATTTGCAAAC TTTCTGCT  
781 CCAGCATGGTGCAGACCTTACCAAAAAAACAGGGATGGAAATAC TCTTTGGATCTTGT  
841 TAAAGATGGAGATACANATATTCAAGATCTGCTTAGGGGAGATGCANNTTTNCTAGATGC  
901 TGCCNANAAGGGTTGTTTTANCCAGATTNAA

>EST assembled

Good protein homology to

gi|3929221 (AF082557) TRF1-interacting ankyrin-related  
ADP-ribose polymerase [Homo sapiens]  
TITLE Tankyrase, a poly(ADP-ribose) polymerase at human telomeres  
JOURNAL Science 282, 1484-1487 (1998)

Longest ORF frame 3 of 258 amino acids

HVASEKAHNDVVEVVVKHEAKVNALDNLGQTS LHRAAXCGHLQTCRLLLSYGCDPNIIISL  
QGFTALQMGNENNVQQLLEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEG  
RQSTPLHFAAGYNRVSVVEYLLQHGADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAV  
VNVADLWKFTPLHEAAAKGKYEICKLLLQHGADPTKKNRDGNTPLDLVKDGDXTXIQDLLR  
GDAXXLDAAXKGCFXQIX

TGCACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACATGAAG  
R2CAAAGGTTAATGCTCTGGATAATCTTGGTCAGACTTCTCTACACAGAGCTGCATNTTGTG  
GNCATCTACAAACCR1TGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACATTATATCCC  
TTCAGGGCTTTACTGCTTTACAGATGF4GGAAATGAAAATGTACAGCAACTCCTCCAAGAGG  
GTATCTCATTAGGTAATTCAGAGGCAGACAGAR4CAATTGCTGGAAGCTGCAAAGGCTGGAG  
ATGTCGAAACTGTAAAAAACTGTGTACTGTTR3CAGAGTGTCAACTGCAGAGACATTGAAG  
GGCGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTGGAAT  
ATCTGCTACAGCATGGAGCTGATGTGCATGCTAAAGATAAAGGAGGCCTTGTACCTTTGC  
ACAATGCATGTTCTTATGGACATTATGAAGTTCAGAACTTCTTGTAAACATGGAGCAGF3  
TAGTTAATGTAGCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAAGGAA  
AATATGAAATTTGCAAACCTTCTGCTCCAGCATGGTGF1CAGACCCTACCAAAAAAACAGGG  
ATGGAAATACTCCTTTGGATCTTGTAAAF2AGATGGAGATACANATATTCAAGATCTGCTTA  
GGGGAGATGCANNTTTNCTAGATGCTGCCNANAAGGGTTGTTTTANCCAGATTNAA

TGCACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACATGAAG  
CAAAGGTTAATGCTCTGGATAATCTTGGTCAGACTTCTCTACACAGAGCTGCATNTTGTG  
GNCATCTACAAACCTGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACATTATATCCC  
TTCAGGGCTTTACTGCTTTACAGATGGGAAATGAAAATGTACAGCAACTCCTCCAAGAGG  
GTATCTCATTAGGTAATTCAGAGGCAGACAGACAATTGCTGGAAGCTGCAAAGGCTGGAG  
ATGTCGAAACTGTAAAAAACTGTGTACTGTTCAGAGTGTCAACTGCAGAGACATTGAAG  
GGCGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTGGAAT  
ATCTGCTACAGCATGGAGCTGATGTGCATGCTAAAGATAAAGGAGGCCTTGTACCTTTGC  
ACAATGCATGTTCTTATGGACATTATGAAGTTCAGAACTTCTTGTAAACATGGAGCAG  
TAGTTAATGTAGCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAAGGAA  
AATATGAAATTTGCAAACCTTCTGCTCCAGCATGGTGCAGACCCTACCAAAAAAACAGGG  
ATGGAAATACTCCTTTGGATCTTGTAAAGATGGAGATACANATATTCAAGATCTGCTTA  
GGGGAGATGCANNTTTNCTAGATGCTGCCNANAAGGGTTGTTTTANCCAGATTNAA

>cip6c1p5F2

TCATTATCTGCTTAGGGGAGATGCAGCTTT  
GCTAGATGCTGCCAAGAAGGGTTGTTTAGCCAGAGCGAAGAAGTTGTCTTCTCCTGATAA  
TGTAATTTGCCGCGATACCCAAGGCAGACATTCAACACCTTTACATTTAGCAGCTGGTTA  
TAATAATTTAGAAGTTGCAGAGTATTTGTTACAACACGGAGCTGATGTGAATGCCCAAGA  
CAAAGGAGGACTTATTCCTTTACATAATGCAGCATCTTACGGGCATGTAGATGTAGCAGC  
TCTACTAATAAAGTATAATGCATGTGTCAATGCCACGGACAAATGGGCTTTACACCTTT  
GCACGAAGCAGCCCCAAAAGGGACGAACACAGCTTTGTGCTTTGTTGCTAGCCCATGGAGC  
TGACCCGACTCTTAAAAATCAGGAAGGACAAACACCTTTAGATTTAGTTTCAAGCGGATGA  
TGTCAGCGCTCTTCTGACAGTAGCCATGCCCCATCTGCTCTGCCCTCTTGTACAAGC  
CTCAAGTGCTCAATGGGTGTGAGAAGCCAGGAGCCACTGCAGATGCTCTCTCTCAGGT  
CCATCTAGCCCATCAAGCCTTTCTGCANCCAGCAGTCTTGACAACCTATTCTGGGAGTTT

>cip6c2p5-F3

GGATGGAAATACTCCTTTGGATCTTGTAAAGATG  
GAGATACAGATATTCAAGATCTGCTTAGGGGAGATGCAGCTTTGCTAGATGCTGCCAAGA  
AGGGTTGTTTAGCCAGAGTGAAGAAGTTGTCTTCTCCTGATAATGTAAATTGCCGCGATA  
CCCAAGGCAGACATTCAACACCTTTACATTTAGCAGCTGGTTATAATAATTTAGAAGTTG  
CAGAGTATTTGTTACAACACGGAGCTGATGTGAATGCCCAAGACAAAGGAGGACTTATTC  
CTTTACATAATGCAGCATCTTACGGGCATGTAGATGTAGCAGCTCTACTAATAAAGTATA

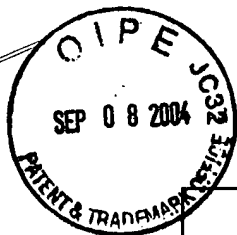


Exhibit B  
09/843,159

6/15/1999

w/ Tank northern blot  
↳ This slide is for Cassen

### Chk1 two-hybrid screening

**Bait: Chk1**

is a protein kinase required for cell cycle arrest in response to DNA damage

**Hit: a novel protein homology to ATP-dependent RNA helicase**  
belongs to the DEAD-box RNA helicase family

The fission yeast *cdc28(+)* encodes a member of the DEAD-box family of putative RNA helicases involved in pre-mRNA splicing and cell cycle progression

a new gene encoding a putative DEAD box helicase have been isolated to suppress uncontrolled mitosis by overexpression *cdc25* in fission yeast  
(Chk1 and 14-3-3 proteins also show up in this screening)

It is interesting to characterize the interaction of Chk1 and the novel RNA helicase and its role in cell cycle control

### Potential targets for further pursuing

p21 hit:	Tankyrase homolog
Traf4 hit:	Cdk liked kinase
hRad9 hit:	PP5
PNCA hits:	a novel helicase
	a human homolog of SNM1
	a novel endo/exo-ribonuclease
Chk1 hit:	an ATP-dependent RNA helicase homolog

**Target validation:**

- full length cloning
- examine the RNA expression in tumor verse normal tissues
- peptide binding library screening in YTH----->functional assay
- generate dominant-negative mutant

**p21 hit: a Tankyrase homolog**

**Tankyrase (a poly(ADP-ribose) polymerase at human telomeres)**

- a protein with homology to ankyrin and to the catalytic domain of ADP-ribose polymerase (PARP)
- is localized to human telomeres
- binds to the telomeric protein TRF1 (telomeric repeat binding factor-1)
- is a positive regulator of telomere length maintenance

SEP 08 2004

Project No. \_\_\_\_\_

Book No. \_\_\_\_\_

Exhibit #C 09/843,169

TITLE Smart HB for #2 (CZPS)

124

From Page 10 RADMARK

7/9/99

SS Syn

polymer HB (100%)  
Smart 0.5% II (9040425)  
primer  
H<sub>2</sub>O

HB (AT)

0.5% (100%)

HB (RH)

0.5% (100%)

SS

ECDS

#2 (RH)

70°C 3' ice

5x 1"

0.1M DTT

DMTP mix

RT

70°C 15h+

+ 50% Tricine-SDTA buffer, 70°C 7' ice.  
(10 mg/ml)

#2 (CZPS)  
upm Nup RII RH

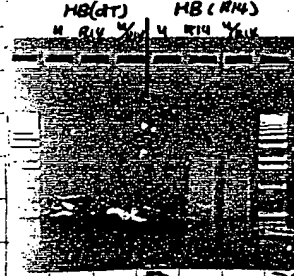
PCR

upm RH upm  
RH

HB (AT) 3x

HB (RH) 3x

Cap 30



7/12/01

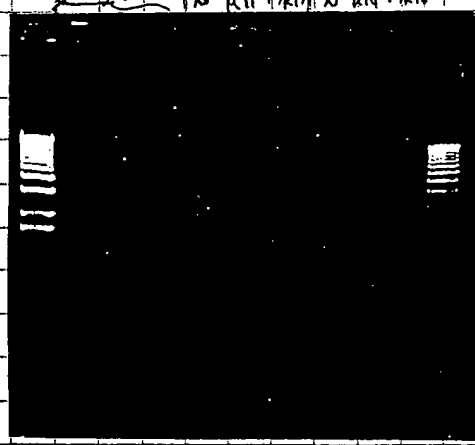
PCR (2P)

primers: Nup RII N/RII

HB(AT) 1P (1/10) 0.5x

HB(RH) 1P (1/10) 10x

Cap 23



X

#2 Cap 1 (RH)  
#2 Cap 2 "

T/A cloning

To Page No. \_\_\_\_\_

Witnessed & Understood by me,

JH

Date

8/2/99

Invented by

SG

Recorded by

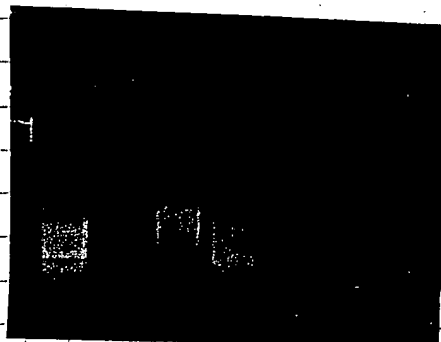
SG

Date

7/9/99

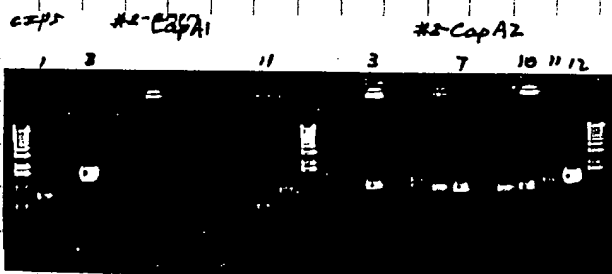
From Page No. \_\_\_\_\_

Repeat 10 but use NdeP1  
 PCR primer: NdeP R11 N/R11  
 template: 1/8 (A7) 2.1  
 1/8 (A14) 2.2  
 Cap30. 2/10  
 X

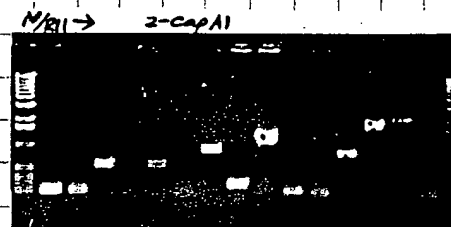


7/13 (2) #2-CapA1 &amp; #2-CapA2

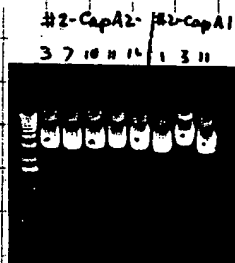
✓ PCR insert screening primer: NdeP/R11



7/19 (2) screening more



7/14 (3) mini plasmid prep:



#2-CapA2-3 (N/R11)

-10

-12

#2-CapA1-3

-11

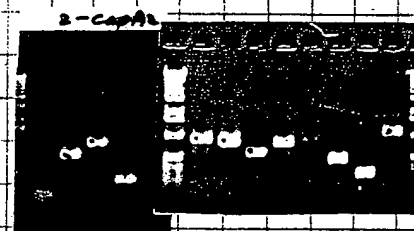
300 ng each

Result  
no sequence7/12 (3)  
to sequence

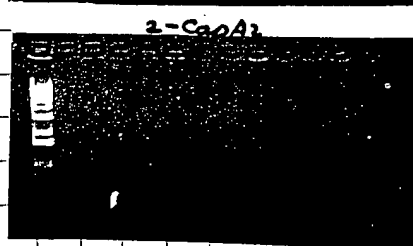
isoform 1

isoform 3

7/12

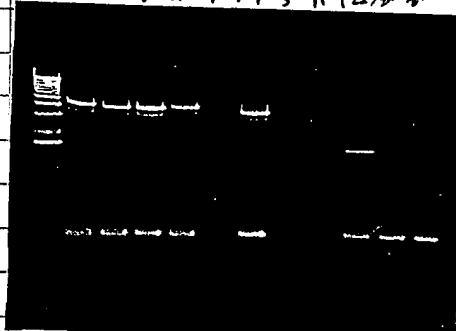


F13/R11 check



#2, PCR check F13/R11!

#2-CapA2- 3 7 10 11 12 | #2-CapA1- 1 3 11 | 2/3, 2/4, 2/5



7/10

To Page No. 137

Witnessed &amp; Understood by me,

JH

Date

8/27/99

Invented by

RS

Recorded by

RS

Date

7/13/99

From Page No. 115

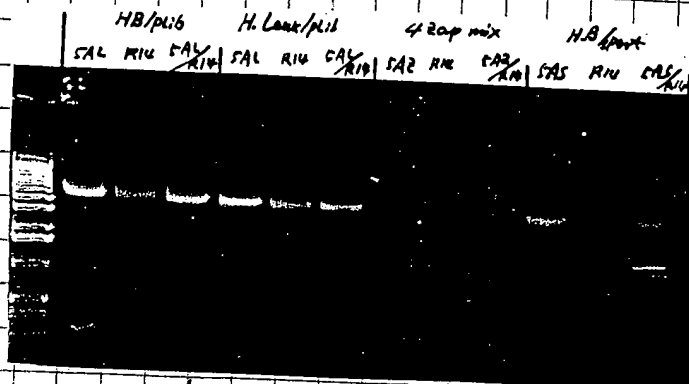
7/1/99 ① 5'-end cloning.

from library

Templates:

- |   |              |         |
|---|--------------|---------|
| ① | HB/plib      | primer  |
| ② | H. Leuk/plib | SAC/R14 |
| ③ | 4zap mix     | SAB/R14 |
| ④ | HB/psport    | SAS/R14 |

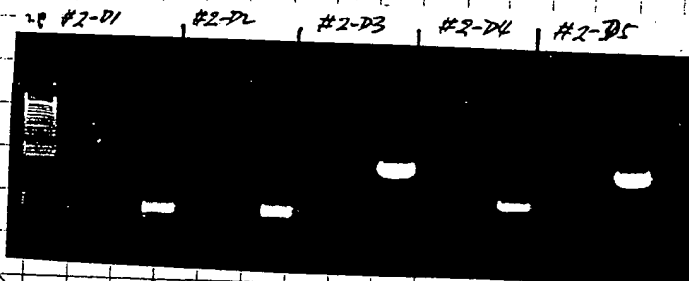
Gap30 (2'10")



7/13/99 ②

2P  
SAB/R11 SAB/R11  
#2-D1  
3  
4  
5  
Cap23

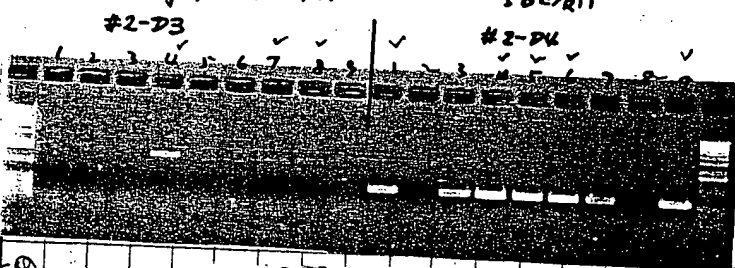
GP GP GP GP  
#2-D1 (SAC/R14) #2-D2 (SAC/R14) #2-D3 (SAB/R14) #2-D4 (SAS/R14)  
#2-D2 " " " "  
insert screening 2-D3, 2-D4 only  
T/A cloning of 2P



7/14

PCR insert screening, primer SAB(2)/R11

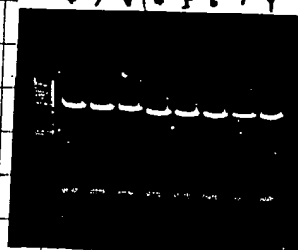
PCR insert screening, primer SAB(2)/R11



GP GP GP GP GP  
#2-E1 (SAB/R14) #2-E2 (SAB/R14) #2-E3 (SAB/R14) #2-E4 (SAB/R14) #2-E5 (SAB/R14)  
X X X X X

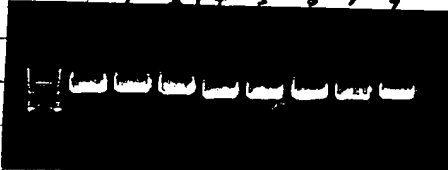
To sequence 7/14 ②

Check insert with F17/R11 (1')

2-D3- 2-D4-  
4 7 9 6 5 6 1 9

7/15 ③

mini prep  
Zul on gel  
Calk  
Core = 300 μg

Witnessed & Understood by me, JH

Date

8/22/99

Invented by

Sy

Recorded by

Sy

Date

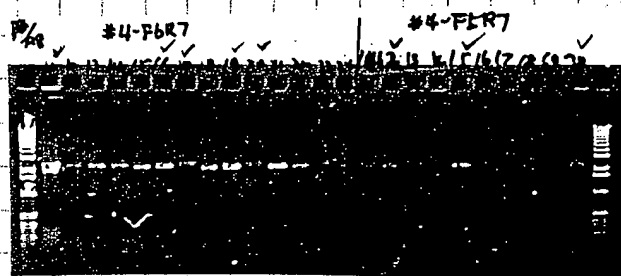
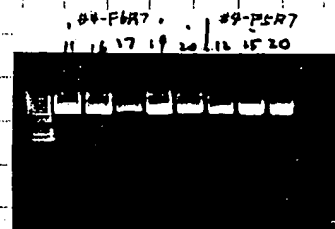
7/13/99

To Page No. \_\_\_\_\_



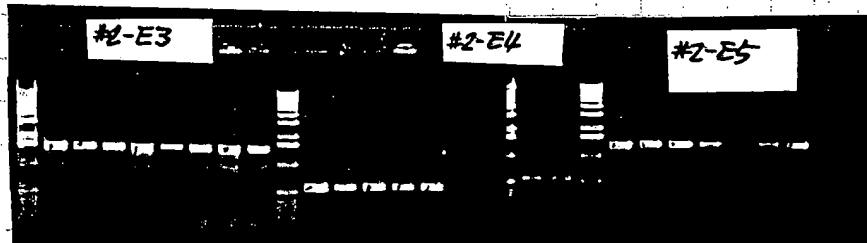
From Page No. 121

7/12/99 ① PCR insert screening again. Last time the amount clones are not enough →  
primer use F5/R8

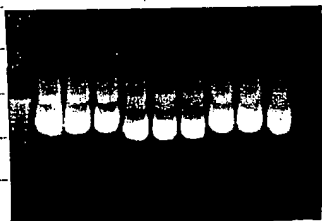
mini plasmid  
prep

#4-F6R7-11 } 7/13  
-19 } to sequence  
-20 }  
#4-F5R7-15 }

7/15/99 ④ Clones PCR insert screening



mini (7/19)



7/20/99 ⑤ 7/13/R11 insert check result: all of them have band.

To Page No. \_\_\_\_\_

Witnessed &amp; Understood by me,

JH

Date

8/24/99

Invented by

SH

Recorded by

SH

Date

7/13/99

From Page No. 127

7/1/99 (2) Compare pH of PCR Buffer -

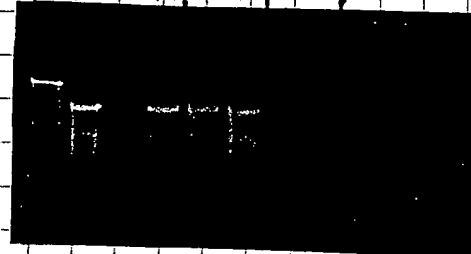
API R14 API R14

template + 100 (Marathon) 300 ng 1 in 25 PCR  
 + 0.5 M HCl + 0.2 M HCl  
 + 1.5 " + 0.5 "  
 + 2.5 " + 0.8 "

Copy  
 successful

HCl 0 0.2 0.5 0.8

API R14 API R14 API R14

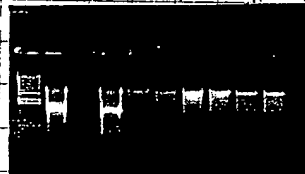


X

Try New buffer &amp; API.

API R14 API R14

API R14 API R14 API R14 New Buff. 3



X

To Page No. \_\_\_\_\_

Witnessed &amp; Understood by me,

JH

Date

8/2/99

Invented by

GJ

Recorded by

GJ

Date

7/15/99

1911 1912

- ②
- |              |   |             |
|--------------|---|-------------|
| HB (CR)      | ✓ | 6/30, pms-7 |
| T+B          | ✓ | RIU         |
| H. Mela      | x |             |
| H. Liver/pl. | ✓ |             |

- { #2-C1-6 (1 kb)  
 (NB) -7  
 -12  
 -18  
 #2-C2-1 (2.6 kb)  
 (F18) -5  
 #2-C3-11 (1.6 kb)  
 (K12) -17  
 -18

- ③ { HB/pl ✓  
 H. Lark/pl ✓  
 4 Zap mix ✓  
 H.B/ps ✓
- 7/2, p126-7  
 R14
- X 1B too small 9/12  
 4x4 →  
 a.k.b. →
- mini & clones  
 but didn't pass F43/R11 check X  
 ∴ no to sequencing  
 give pett gp. to F4
- X too more colony plate
- #2-D3 (H. Lark)  
 #2-D4 (4 Zap mix)  
 #2-DX (HB/pl.)

2. ~~2. [REDACTED]~~

- ① ~~Sp~~ myself. x 7/6, p123, 128  
HB RUC { Normal Prof  
different PH prob  
C. Newbusher
- ② Clotback Marathon Ready 7/6, p119  
{ H. Fetal Brain x  
H. Fetal Liver x  
H. Leukocyte x

X primer & adaptor problem.

✓3 ~~CONFIDENTIAL~~ 1957 7/9 pp4-5.

- 1 HB, primer & T ✓  
1 HB, " R14 X

- #2-CapA1-3 (1.5 kb) ✓ isoform 1  
-11 (0.5 kb) ✓ isoform 3  
#2-CapA2-3 (1 kb)  
-10 ✓  
-12 (1.2 kb) ✓ no seq

(~~Class~~ F13/111 check)

- #2-CapA1-29 (1 Kb) ✓  
-33 (2 Kb) ✓  
-34 (2.2 Kb) ✓  
#2-CapA2-26 (3 Kb) ✓  
-29 (2 Kb) ✓

7/20 p137

Result. got 2 isoform from Smart RACE. \* got isoform from Library method.  
But Marathon did work.  
7/22 finish it.

TITLE

CZPS. #2

Project No. \_\_\_\_\_

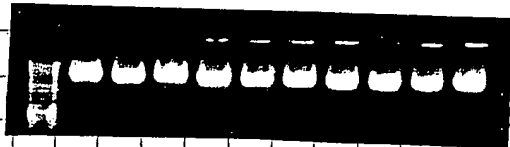
Book No. \_\_\_\_\_

137

From Page No. 125

← min prep. 2x each

~ conc = 200 ng/μl



→ F13/R11 insert check again

# 2-CapA1-29

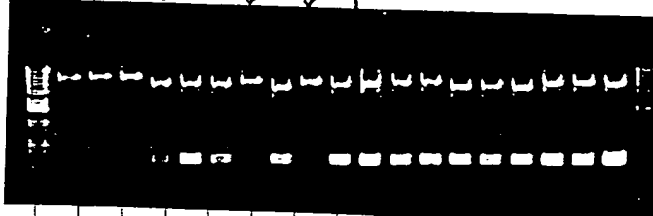
33 } to sequence 7/20 (2)

34

2-CapA2-26

29

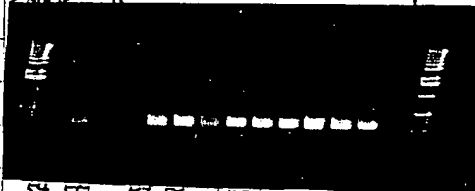
F13/R11  
CZPS  
2-CapA1-29  
-33  
-34  
2-CapA2-26  
-33  
-34  
-35  
-36  
-37  
-38  
-39  
-40  
2-B3-1  
-2  
-4  
2-B4-1  
-3  
-4  
2-E5-1  
-2  
-3



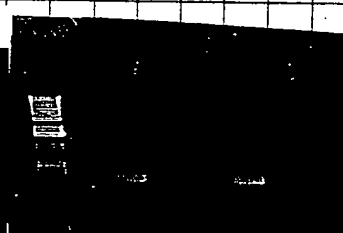
7/21 (3) Pick 20 clones from #2-CapA1

PCR insert screening Nup/R11 & F13/R11

F13/R11



34



N/R11 per

41 43



PCR screening 2x per assay

#2-CapA1-50

(N/R11)

#2-CapA1-60

mini

(Seq 1/35)

CZPS #2-CapA1-60 to sequence (7/21)

To Page No. \_\_\_\_\_

Witnessed & Understood by me,

JH

Date

8/17/99

Invented by

SY

Recorded by

SY

Date

7/21/99



4931  
FLEHR, HOBACH, TEST  
ALBRITTON & HERBERT

1999 JUL 22 AM 9.02

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July 20, 1999

RIGEL, INC.

VIA FEDERAL EXPRESS

Ms. Robin Silva  
Flehr, Hobach, Test, Albritton, & Herbert  
4 Embarcadero Center, Suite 3400  
San Francisco, California 94111-4187

*Per RMS - OPEN  
AS USUAL*

Re: Provisional Patent Applications.

Dear Ms. Silva,

Per Brian Cunningham's request, enclosed with this letter are eight packages of information generated by Dr. Ying Luo in preparation for provisional patent application filings. Each package pertains to a different genetic sequence that Rigel believes may be commercially useful. Each package contains relevant scientific materials, journal references and abstracts of proposed gene functions.

Please file a provisional patent application for each document.

If you have any questions, please call me at 650-624-1106.

Respectfully yours,

Nicole A. Verona  
Rigel Pharmaceuticals, Inc.

Exhibit DE 09/843,141

FLEHR, HOBACH, TEST  
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Ms. Robin Silva  
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4 Embarcadero Center, Suite 3400  
San Francisco, California 94111-4187

ORIGINAL Diskette in  
P-68287

Re: Provisional Patent Applications.

Dear Ms. Silva,

It was a pleasure to meet you today. I'm sorry that I did not see you leave; I had intended to give you these diskettes before the end of our meeting.

On these diskettes are the documents that we reviewed earlier. The new document that Ying gave to me today will be ready on Monday.

If you have any questions, please call me at 650-624-1106.

Respectfully yours,

*Nicole Verona*

Nicole A. Verona  
Rigel Pharmaceuticals, Inc.

Exhibit B F 09/843,149

DOCKETING/BILLING SYSTEM FILE INFORMATION  
(Patent/Design Patent)

Date: July 26, 1999 File No.: A-68292  
Client: Rigel Pharmaceuticals Access Code: 4931  
Client Attorney: DJB/RMS/DAV  
Ref. No.:

New ☒ Update ☐ Close ☐  
Parent ☐ Div. ☐ CPA ☐ CIP ☐

Subject Description

Title: TANKYRASEH, A Cell Cycle Protein

Inventors: Ying Luo

Serial No.:  
Filing Date:

Patent No.:  
Issue Date:

Assignee:

Related Files:

If Foreign file, please provide corresponding U.S. Serial Number  
or Patent Registration Number.

Misc. (Include any action items and due dates here!):

Submitted by: Gail Clark Date: July 26, 1999

cc: Accounting  
Docketing - Foreign  
Docketing - US

2x hint AG 09/843, 149

From: Nicole Verona <NVerona@rigel.com>  
To: "'dvance@flehr-iplaw.com'" <dvance@sfpo.fhtah.fleh...  
Date: 8/30/99 4:01pm  
Subject: FW: FW: info

Dear Dolly,

I forwarded your questions to Ying Luo and this is the response I received from him. I hope this helps. Also, I've got copies of the TNIK manuscript figures that you need. Would you like me to fax them to you?

Nicole

-----Original Message-----

From: Ying Luo [mailto:yluo@rigel.com]  
Sent: Sunday, August 29, 1999 2:44 PM  
To: Nicole Verona  
Subject: Re: FW: info

PAN is from PCNA screening. tankyraseH is from CIP screening. CIP is also called p21. R0101 has an entry in GenBank with full length sequence with a name called KIAA0101. No functional annotation about R0101. PP5 was cloned and published before. The novelty is we can link PP5 to RAD9, a cell cycle checkpoint control protein. You should have all figures of TNIK manuscript already. TNIK nucleotide sequences are attached. PAN nucleotide sequence is already in Genbank.

Ying

At 03:21 PM 8/26/99 -0700, you wrote:

>Hi Ying!

>

>Here are some of the questions I need to discuss with you.

>

>Nicole

>

>-----Original Message-----

>From: Dolly Vance [mailto:dvance@flehr-iplaw.com]  
>Sent: Friday, August 20, 1999 1:42 PM  
>To: nverona@rigel.com  
>Subject: info

>

>

>Dear Nicole,

>Hope you're well. Here's a complete list of what I am missing from the  
>initial 9 disclosures.

>

>1) The names of binding partners (if any actual) for CAH and  
>tankyraseH.

>2) The nucleic acid and amino acid sequences for PAN and TNIK  
>(actually, all figures that go with the manuscript for TNIK).

>3) Please confirm that R0101 and PP5 are NOT novel, and that all  
>others are novel.



>

>Thanks. Dolly

>P.S. I understand your hours are reduced. Any chance you can give me a

>time frame for providing the above information? Thanks again, Dolly

>

RIGEL

FLEHR, HOHBACH, TEST,  
ALBRITTON & HERBERT

1999 OCT -1 AM 10:09

RECEIVED

Exhibit H 09/843 149

RIGEL, INC.

September 30, 1999

Ms. Dolly Vance  
Flehr, Hohbach, Test, Albritton and Herbert LLP  
4 Embarcadero Center, Suite 3400  
San Francisco, California 94111-4187

Dear Dolly,

Enclosed are documents pertaining to the cell-cycle patent applications that you requested.

The documents include:

1. TankyraseH abstracts involving TRF, P21, and PARP
2. TankyraseH nucleotide sequence alignment report
3. TankyraseH amino acid sequence alignment report
4. R0101 figures with corrected CDK 2, 3, and 4 labels
5. Mkinase nucleotide and amino acid sequences with its kinase domain and nuclear localization sequence (NLS) highlighted

Additional information will be sent to you next week.

Please call or email me if you have any questions.

Sincerely,

*Nicole Verona*

Nicole Verona

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